Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Draft Guidance for Industry and FDA

Draft Guidance – Not for Implementation

This guidance document is being distributed for comment purposes only.
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When final this document will supersede "Guidance Criteria for Cyclosporine PMAs" dated January 24, 1992

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

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Division of Clinical Laboratory Devices
Office of Device Evaluation

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Preface

Public Comment

For 60 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, *5630* Fishers Lane, Room 1061, (HFA-305), Rockville, MD *20852.*

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Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Draft Guidance for Industry and FDA

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

1. Background

This draft guidance was developed as a special control guidance to support the reclassification of the cyclosporine and tacrolimus assays into class II. The device is intended to quantitatively determine cyclosporine or tacrolimus concentrations as an aid in the management of transplant patients receiving therapy with these drugs. This draft guidance will be issued in conjunction with a Federal Register notice announcing the proposal to reclassify this device type. This guidance is issued for comment purposes only. If a final rule to reclassify this device type is not issued, this guidance will not be issued as a special control.

FDA is proposing this action after reviewing reclassification petitions from industry for cyclosporine test systems. The agency is including tacrolimus test systems in the proposed reclassification because of the similarities between these two test systems in terms of indications for use, assay technologies, potential risks and considerations for demonstrating performance characteristics. When final, this guidance will replace the guidance "Guidance Criteria for Cyclosporine PMA's."

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the cyclosporine and tacrolimus assays. Thus, a manufacturer who intends to market a device of this generic type must (1) conform with the general controls of the Federal Food, Drug & Cosmetic Act, including the 5 1 O(k) requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with cyclosporine and tacrolimus assays, and (3) receive a substantial equivalence determination from FDA prior to marketing the device.

This special control guidance document identifies the classification, product code, and classification identification for the cyclosporine and tacrolimus assays. In addition, it lists the risk to health identified by FDA and serves as the special control that, when followed and combined with the general controls, will generally address the risks associated with this generic

device type and lead to a timely 5 1 O(k) review and clearance. For the specific content requirements of a 5 10(k) submission, you should refer to 21 CFR 807.87 and other agency documents on this topic, such as "5 10(k) Manual - Premarket Notification: 5 1 O(k) - Regulatory Requirements for Medical Devices," http://www.fda.gov/cdrh/manual/5 1 Okprtl .html.

Device manufacturers may choose to submit an Abbreviated 5 1 O(k) when: (1) a guidance exists, (2) a special control has been established, or (3) FDA has recognized a relevant consensus standard. FDA believes an Abbreviated 5 10(k) is the least burdensome means of demonstrating substantial equivalence once a Class II Special Controls Guidance Document has been issued. **See** also **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance,** http://www.fda.gov/cdrh/ode/parad51O.html.

An Abbreviated 5 1 O(k) must include the required elements identified in 2 1 CFR 807.87, including a description of the device, the intended use of the device, and the proposed labeling for the device. An Abbreviated 5 1 O(k) should also include a summary report. In an Abbreviated 5 1 O(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g).

The summary report should briefly describe the methods or tests used and the acceptance criteria applied to address the risks identified in this guidance as well as any additional risks specific to your device. When a suggested test method is followed, a simple reference to the method will be an acceptable description. If there are any deviations from a suggested test method, you should provide more detailed information in the summary report to characterize the particular deviation. The summary report should also either (1) briefly present the data resulting from each test in tabular form or (2) describe the acceptance criteria to be applied to the test results. (See also 21 CFR 820.30 Subpart C Design Controls for the Quality System Regulation.)

2. Scope

The scope of this guidance is limited to the following devices:

FDA identifies the generic cyclosporine assays classified under 21 CFR 862.xxxx and generic tacrolimus assays classified under 21 CFR 862.xxxx [to be designated, if a final rule is published]. The product codes are:

MKW Cyclosporine

MAR Cyclosporine And Metabolites Serum Assay

LTB Cyclosporine Radioimmunoassay

MGU Fluroesence Polorization Immunoassay For Cyclosporine

MGS High Performance Liquid Chromatography For Cyclosporine

MGV Radioimmunoassay For Cyclosporine

MLM Enzyme Immunoassay, Tracrolimus

This generic type of device includes immunoassays and chromatographic assays for cyclosporine and tacrolimus.

3. Risks to Health

There are no *known direct* risks to patient health. However, failure of the test to perform as indicated or error in interpretation of results may lead to improper patient management. A falsely low cyclosporine or tacrolimus measurement could contribute to a decision to raise the dose above that which is necessary for therapeutic benefit. This could result in increased risk of toxicity from an elevated drug level. A falsely high cyclosporine or tacrolimus measurement could contribute to a decision to decrease the dose below that which is necessary for immunosuppression. This could result in increased risk of rejection of the transplanted organ. Moreover, no firm therapeutic range exists for cyclosporine or tacrolimus [1-3]. Optimal ranges for patients depend upon many factors such as transplant type, sensitivity of patient, co-administered drugs, and time post-transplant as well as metabolite cross-reactivity of the specific commercial assay used. Therefore, use of assay results to adjust a treatment regimen without consideration of other clinical factors could pose a risk.

FDA has identified the following risk to health generally associated with the use of the cyclosporine and tacrolimus assays in'the table below. You should also conduct a risk analysis to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. The measures recommended to mitigate the identified risk is given in this guidance, as shown in the table below. (If you elect to use an alternative approach to address a particular risk, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the alternative approach.)

Identified risk	Recommended mitigation measures
improper patient management	Sections 6 and 7

4. Controls

FDA believes that the controls in the following sections of this guidance, when combined with general controls, will address the identified risk to health associated with the use of cyclosporine and tacrolimus assays. Manufacturers should demonstrate that their device complies with either the specific recommendations of this guidance or with an alternate means to address the above identified risk to health and to provide reasonable assurance of the safety and effectiveness of the device. If you elect to use an alternative approach to address a particular risk, you should provide sufficient detail to support the alternative approach.

5. Abbreviated 510(k) Content

An Abbreviated 5 1 O(k) that relies on a Class II Special Controls Guidance Document should contain the following.

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 5 1 O(k) and cite the title of the specific Class II Special Controls Guidance Document.

Items Required Under 21 CFR' 807.87

The items required under 21 CFR 807.87 are:

- Description of the device. You should also include a complete discussion of performance specifications, description of methodology, reagents, enzymes or 'antibodies and, when appropriate, detailed, labeled drawings of the device.

- Intended use of the device. You should also include **an Indications for Use Enclosure,** see http://www.fda.gov/cdrh/ode/indicate.pdf for the recommended format.

- Proposed labeling for the device.

- Summary report. A summary report should describe how the Class II Special Controls Guidance Document was used to address the risks associated with the particular device type. The summary report should contain:

  . Risk analysis.

  - Description of device performance requirements.

  - Discussion of the features and functions provided to address the risks identified in this Class II Special Controls Guidance Document, as well as any additional risks identified in your risk analysis.

  - For each performance aspect identified in Section 6, you should briefly discuss each protocol and your acceptance criteria. When describing protocols, you should outline deviations from the guidance or specifics that you have incorporated. The summary report should also either (1) briefly present the data resulting from each test in tabular form or (2) describe the acceptance criteria to be applied to the test results. If the device does not meet the acceptance criteria, the device may not be marketed, and a new 5 1 O(k) submission will need to be submitted and cleared by the FDA.

  - If any part of the device design or testing relies on a recognized standard, the summary report should include: (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a

declaration of conformity to the standard. Testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information, see FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA,** http://www.fda.gov/cdrh/ode/guidance/113 1 .html.

If it is not clear how you have addressed the risks identified by FDA or by your risk analysis, we may request additional information about the protocols or aspects of the device's performance characteristics. We may also request additional information, if we need it to assess the adequacy of your acceptance criteria.

As an alternative to submitting an Abbreviated 510(k), you may submit a traditional 510(k) that provides all of the information and data described in this guidance. A traditional 5 1 O(k) should include all of your protocols, data, analyses, and conclusions.

6. Performance Characteristics

General Study Recommendations

Whenever possible, you should include patient samples or sample pools, derived from the intended use population (i.e., patients taking cyclosporine or tacrolimus) for the analytical protocols described below. Minimally, samples from patients taking cyclosporine or tacrolimus should be included in the precision and recovery studies. This is important because patient samples reflect the relevant proportions of free and bound drug, metabolites, and other drugs commonly co-administered to transplant patients and therefore help demonstrate robustness of the assay.'

Although spiked samples can be used to supplement the studies, FDA cautions against using spiked samples as the only matrix in the evaluations, because spiked samples may not provide an accurate assessment of the performance characteristics. FDA recommends that you do not use hemolysates (often found in control or calibrator material) in the analytical studies, because these specimens may not test the effects of all preparatory steps on test performance.

You should perform all of your analytical protocols in accordance with the procedures you recommend to users in the package insert, in order to reflect performance expected by the user. Therefore, ensure that all steps (e.g., cell lysis, extraction, centrifugation) are included in each of the analytical studies and that all manufacturer recommended quality control and calibration procedures are followed.

So that acceptance criteria can be best interpreted during review, you should provide appropriate specifics concerning protocols. These specifics are also necessary to aid users in interpreting information in your labeling. For example, when referring to NCCLS evaluation protocols or guidelines, you should indicate which specific aspects of the protocols or guidelines you followed.

In studies using spiked samples, you 'should provide information about purity of drugs, metabolites, or potential interferents used, as well as the type of sample that drug is spiked into.

Whole blood is the matrix recommended in consensus statements from major scientific groups associated with organ transplantation [1-4]. For assays intended for use in other matrices, FDA believes you need to demonstrate a strong correlation with the analyte in whole blood using specimens from patients on drug therapy. Before initiating a study of this type, you should contact DCLD to discuss your protocol.

Studies typically expected for current cyclosporine and tacrolimus instrument-based assays used in central clinical laboratories are described below. Depending on indications for use, assay methodology, and test performance compared to currently marketed devices, additional studies, including clinical studies, may be appropriate.

Specific Performance Characteristics

You should assess the following performance characteristics, in order to document performance and properly label your device in conformance with 2 1 CFR 809.1 O(b)(12). In an Abbreviated 5 1 O(k), you may briefly present the data resulting from each test in tabular form' **or** (2) describe the acceptance criteria to be applied to the test results. In a traditional 5 1 0(k), you should present the data for each of these performance characteristics.

Precision

You should characterize within-run, and total precision according to guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices;" Approved Guideline (1999) National Committee for Clinical Laboratory Standards (NCCLS), Document EP5-A. That document includes guidelines for experimental design, computations, and format for statement of claims. You should evaluate, precision at relevant drug levels, including near medical decision levels and levels near the limits of reportable range. For example, for an assay with a reportable range between 40 ng/ml and 400 ng/ml, appropriate levels for testing would include 40,200, and 400 ng/ml. You should evaluate whole blood samples from patients taking cyclosporine or tacrolimus during these studies. The description of your protocol and acceptance criteria in the summary report should include the items listed below:

- sample types
- point estimates of the concentration
- standard deviations of within-run and total precision
- sites at which precision protocol was run
- number of days, runs, and observations.

[1] unless a Class II Special Controls Guidance Document recommends scatterplots or other graphical representations.

You should also identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant and which were varied during the evaluation. You should describe the computational methods, if they are different from that described in NCCLS EP5-A.

Recovery

As a measure of accuracy, you should characterize the percent recovery of cyclosporine or tacrolimus. Typically, these studies involve spiking known amounts of cyclosporine or tacrolimus into samples that are either negative for these drugs or contain known drug concentrations. You should include spiking into samples from patients taking cyclosporine or tacrolimus, as part of the study. Final concentrations of the spiked samples should span a significant part of the reportable range and include potential medical decision levels.

You should evaluate replicates of each concentration or sample. You should choose the number of replicates so that any clinically significant differences observed will be statistically significant. Description of the study protocol in the summary report should include:

- sample types and concentrations
- materials used for spiking
- number of replicates
- definition or method of calculating recovery.

When reporting acceptance criteria in the summary report, you should indicate the range of recoveries for each concentration level evaluated since this approach is more informative than describing only average recoveries at each concentration level.

Linearity

You should characterize the linear range of the assay by evaluating samples whose concentration levels are known relative to each other. The sample concentrations should be evenly distributed across the reportable range of the assay. The appropriate number of replicates and concentration levels depends on the reportable range of the assay. For tacrolimus assays, you should include a minimum of four replicates at five concentration levels. For cyclosporine assays, which typically span wider concentration ranges, you should evaluate additional concentration levels (for example, levels in increments of 50 ng/ml). Diluted patient sample pools are appropriate samples for the study. Evaluation of the Linearity of Quantitative Analytical Methods, Proposed Guideline NCCLS Document EP6-P describes a protocol for sample preparation and value assignment as well as a format for statement of claims. You should: evaluate the goodness of fit of the linear model using chi-square or ANOVA, as appropriate.

The description of your protocol and acceptance criteria in the summary report should include sample types and preparation, slope of the estimated line and the degree of deviations

(biases) from the estimated line that were observed or that are considered acceptable for various concentration levels. Often these deviations can be best described by listing observed or acceptable values relative to expected values for each level evaluated. FDA recommends this approach.

You should provide information on how samples outside the reportable range should be treated. If you recommend that users dilute samples that are above the reportable range, you should provide a specific protocol for dilution and include in the summary report a validation of that protocol. You should also clarify how samples with concentrations outside the range of linearity are reported to the user.

Sensitivity

You should characterize the limit of quantitation (functional sensitivity) of the assay, which is the lowest drug concentration that can be reliably measured by the assay. Often this is considered the concentration at which the inter-assay coefficient of variation is not greater than 20%. This information can be determined during the precision studies described above. Clarify in the summary report how measurements below the level of sensitivity are reported to the user. Any additional measures of sensitivity, such as limit of detection that you include should be clearly defined in the summary report.

Specificity for parent compound

As a measure of assay specificity, you should characterize cross-reactivity with cyclosporine or tacrolimus metabolites. Metabolites that should be included for cyclosporine specificity studies are AM1, AM4n, AM9, AM19, AM1c, AM1c9 (see reference 7, figure 2 for definitions). Metabolites that should be included for tacrolimus specificity studies are MI, MII, MIII, MIV, MV, MVI, MVII, MVIII (see reference 2, table 3 for definitions). Typically, these studies involve spiking the metabolites into drug-free whole blood pools to final concentrations of at least 1000 ng/ml for cyclosporine or 40 ng/ml for tacrolimus. You should evaluate replicates of spiked samples. Materials of high purity should be used for these protocols, whenever available. You should describe the purity of metabolites used.

The description of your protocol and acceptance criteria in the summary report should include description of types of samples used for spiking, number of replicates, concentration of metabolite, computation or definition of cross-reactivity used and percent cross-reactivity for each metabolite.

Interference

You should characterize the effects of potential interferents on assay performance. Potential sources of interference that you should test include the following:

(1) endogenous compounds, such as (where applicable, the recommended upper limit concentration is given in parentheses):

- bilirubin (60 mg/dL)
- triglycerides (1500 mg/dL)
- cholesterol (500 mg/dL)
- uric acid (20 mg/dL)
- rheumatoid factor (500 IU/ml)
- hematocrit (15-60%)
- albumin (12g/dL)
- gamma globulin (12g/dL)
- human anti-mouse antibodies, HAMA

(2) commonly co-administered drugs including, but not limited to:

- cyclosporine
- tacrolimus
- mycophenolic acid and its metabolite, MPAG
- rapamycin
- cornmon over-the-counter drugs

(3) anticoagulants or preservatives with which the sample is likely to come in contact, such as EDTA.

When testing these interferents, you should adjust cyclosporine or tacrolimus concentrations in the sample to near medical decision level. Typically, interference studies involve adding potential interferent to the sample containing the drug and determining any bias in recovery of cyclosporine or tacrolimus, relative to a control sample (to which no interferent has been added). Appropriate experimental designs, including guidelines for selecting interferents for testing, are described in detail in "Interference Testing in Clinical Chemistry; Proposed Guideline" (1986) National Committee for Clinical Laboratory Standards, Document EP7-P which proposes the following recommendations.

- For endogenous substances, test up to the highest concentration expected based on experience with the intended use population. Interference studies using samples naturally high in the endogenous compound being tested can be informative and this approach should be considered when such samples are available.

- For drug levels, test up to levels lo-fold higher than highest concentration reported following therapeutic dosage.

- For specimen additives, test up to levels five times the recommended concentration.

If you observe interference at the concentration levels tested, you should test lower levels in order to determine the lowest concentration that could cause interference. You should test replicate samples in these protocols.

The description of your protocol and acceptance criteria in the summary report should include the following items:

- types and levels of interferents tested
- sample type (e.g., spiked whole blood pools, samples naturally high in endogenous compounds)
- concentrations of cpclosporine or tacrolimus in the sample
- number of replicates tested
- definition or method of computing interference.

When reporting acceptance criteria in the summary report, you should identify any observed trends in bias (i.e., negative or positive) and indicate the range of observed recoveries in the presence of the particular interferent. This approach is more informative than listing average recoveries alone.

For substances listed as non-interfering, you should state the criteria on which this is based, e.g., inaccuracies due to these substances are less than x % at cyclosporine concentrations of 200 ng/ml. If any potential interferents are known from the literature or other sources to interfere with the test system, you should include them in the labeling. For these known interferents, you may not need to perform any additional interference testing with them.

Specimen collection and handling conditions

You should substantiate the labeled recommendations for specimen storage and transport, by assessing whether the device canmaintain acceptable performance (e.g., precision, accuracy) over the storage times and temperatures (including freeze/thaw cycles) recommended to users. An appropriate study includes analysis of sample aliquots stored under the conditions of time, temperature, or allowed number of freeze/thaw cycles recommended in the package insert. You should state the criteria in the summary report for acceptable range of recoveries under the recommended storage and handling conditions.

Method comparison

Currently marketed cyclosporine ‘and tacrolimus assays vary significantly in terms of cross-reactivity patterns with metabolites whose therapeutic and toxic effects are not well-defined [9-13]. Therefore, you should compare the new assay to a candidate reference method, specific for the parent compound. Carefully validated high performance liquid chromatography methods that measure parent drug specifically, such as methods described in references 14- 16, should be used as reference procedures. In addition, for immunoassays, it may be beneficial to conduct a comparison study to a predicate device using an immunoassay technology similar to the new device.

You should follow the guidelines provided in the document, Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (1995) National Committee for Clinical Laboratory Standards, Document EP9A concerning experimental guidelines and

statement of claims. You should evaluate patient samples with drug concentrations distributed across the reportable range of the assay. Cyclosporine is currently indicated for heart, liver and kidney transplant patients. Tacrolimus is indicated for kidney and liver tranplant patients. Since variations in assay performance have been observed for the various organ transplant types [9-11], you should evaluate samples from patients with heart, liver and kidney transplants for cyclosporine test systems and samples from liver and kidney transplant patients for tacrolimus test systems.

Appropriate sample size depends on factors such as precision, interference, range, and other performance characteristics of the test. The number of patients should also be large enough so that inter-individual variation would be observed. A statistical justification to support the study sample size should be provided in the protocol description in the summary report. We expect that the sample size target, however supported, will include a minimum of 50 samples from 50 *individualpatients* for each organ transplant group, for which the drug and test are indicated (i.e., a minimum of 100-l 50 samples total).

If you choose to include additional multiple measurements from individual patients, you should summarize your results of appropriate statistical analyses such as Analysis of Variance, Generalized Estimating Equations, or Bootstrapping, to account for correlation of repeat measurements within patients in the study. If multiple measurements from individuals are included they should range over time, post-transplant. FDA believes it is helpful for samples from patients undergoing various treatment regimens to be included, and therefore recommends including samples from multiple geographic sites or clinical centers.

For your acceptance criteria to be properly interpreted during the review processyou should provide all relevant information on the sample population in the summary report and the package insert.

Information on sample population should include the number of:

- individual patients represented by the samples;
- data points;
- clinical sites; and
- samples from each transplant type.

You should state any specific selection criteria for samples. You should also indicate whether samples were collected from patients with specific clinical outcomes, or from centers using atypical or novel drug regimens. Factors such as age range (e.g., adults), time post-transplant (e.g., chronic, acute), and time of blood draw with respect to drug administration (e.g., trough, 2 hour) can influence drug-to-metabolite ratios and consequently, assay bias [17,181. Therefore, you should describe these features of the sample population. You should clarify in the summary report the HPLC method used, and include references to validation of the procedure from the literature.

You should conduct separate analyses of data for each organ transplant group for which the test is indicated. If samples evaluated in the study include both trough and other times of blood draw relative to drug administration, you should conduct separate analyses for these groups as well. When providing the results of the method comparison study, you should include the following information:

- Scatter-plots of the new assay versus the reference (e.g., HPLC) method. The plots should contain all data points, the estimated regression line and the line of identity. Data points in the plot should represent individual measurements.

- A description of the method used to fit the regression line and results of regression analysis including, the slope and intercept with their 95% confidence limits, the standard error of the estimate (calculated in the y direction), and correlation coefficient should be included in the summary report. In cases where parameters are. not consistent throughout the reportable range, estimates of more than a single range may be appropriate. If the comparator, as well as the new assay is subject to measurement error, a regression method such as the Deming method may be appropriate, rather than Least Squares [19].

- To illustrate the degree of inter-individual variations, you should include graphs of difference in measurements (i.e., new device minus reference HPLC method) versus the reference HPLC method. Appropriate representations include a bias plot of difference in measurements (y - x) versus the reference method (x), as recommended in NCCLS EP9 [20], or versus the mean of y and x, as recommended by Bland and Altman [21].

In the 5 1 O(k) summary report, you should explain how the acceptance criteria for the method comparison study support substantial equivalence. If you are submitting a traditional 5 1 O(k), you may also choose to include line data, if this would be beneficial for clarification of the protocol or results.

Studies at external sites

You should validate performance at laboratory sites other than that of the manufacturer. FDA recommends that you include this validation, at two external sites, as part of the method comparison study described above, Data from individual sites should initially be analyzed separately to evaluate any inter-site variation and results of the analysis should be included in the 5 1 O(k) summary report. Method comparison results from the individual sites can be pooled in the package insert, if you demonstrate that there are no significant differences in results among sites.

Calibrators

You should provide the following information about the calibrators in the assay kit in your summary report:

- Protocol and acceptance criteria for real-time or accelerated stability studies for opened and unopened calibrators.

- Protocol and acceptance criteria for value assignment and validation, including any specific instrument applications or statistical analyses used.

- Identification of traceability to a domestic or international standard reference material.

- Protocol and acceptance criteria for the transfer of performance of a primary calibrator to a secondary calibrator.

For information about calibrators marketed separately as class II devices under 862.1150, see the guidance "Abbreviated 5 1 Ok Submissions for *In Vitro* Diagnostic Calibrators," http://www.fda.gov/cdrh/ode/calibrator.html.

7. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Final labeling for *an in vitro* diagnostic device must comply with the requirements of 21 CFR 809.10 before being introduced into interstate commerce, however, final labeling is not required for 5 1 O(k) clearance. The following suggestions are aimed at assisting manufacturers in complying with 2 1 CFR 809.10.

Specimens

You should discuss the importance of consistency of time of blood draw with respect to last dose, as well as time of day. Consistency of time of day may be important considering reports that Cyclosporine A concentrations display a circadian rhythm with evening trough levels being significantly lower than morning trough levels [22].

You should discuss any limitations or instructions related to the specimen, such as appropriate matrices or anticoagulants (in most cases, EDTA).

You should provide instructions concerning preserving integrity of the specimen, such as temperatures for collection, transport, storage (short and long term) and procedural steps of the assay necessary to maintain assay performance. Storage conditions recommended to the user should be based on the conditions you have validated for your test system. You should clearly define any acceptance criteria that you apply in determining the recommended storage conditions (e.g., inaccuracies due to instability under these conditions are less than 10% for 95% of samples tested). Additional information on storage conditions based on literature can be cited if they are applicable to your test system.

Assay procedure

You should include appropriate time limits and temperature requirements for the procedural steps. Whenever applicable, you should describe expected appearance of the specimen through various procedural steps and advise users of any signs that may indicate whether the assay is proceeding correctly.

You should advise users how to proceed for samples with concentrations above the highest calibrator. If you instruct users to dilute these samples, you should provide a validated procedure for the dilution.

You should advise users of any steps that can be taken to minimize effect of carryover, or other causes of bias or n-reproducibility, based on procedures you have validated for your test system.

Quality control

You should advise users of the specifics of calibration and quality control procedures necessary to ensure the performance claims of the system and include instructions for interpretation of the results of quality control samples, satisfactory limits of performance and instructions on how to proceed if limits of performance are not satisfied. You should include recommendations for appropriate quality control specimens. Consensus documents recommend that whole blood assays should employ whole blood controls with well-characterized drug preparations [4].

Limitations

You should include the following limitation, when appropriate for your device type.

Patients with abnormal liver function, elevated bilirubin levels, unexpectedly high drug values, or increased time post-therapy may have impaired drug elimination and metabolite accumulation. For such patients, use of this assay may be supported with a method more specific for the parent compound (e.g., HPLC).

You should identify any exogenous or endogenous factors known to affect results and describe the effect on results (e.g., highly lipemic samples may cause falsely low results).

A number of drug interactions with cyclosporine and tacrolimus are mediated at the metabolic level. References listing drugs currently known to interact with metabolism of cyclosporine and tacrolimus should be cited in an appropriate section of the package insert.

Therapeutic ranges

Since therapeutic ranges vary depending on the methodology used as well as the clinical state of the individual, stating one specific therapeutic range is usually not appropriate for current cyclosporine and tacrolimus assays.

You should include cautionary explanations concerning the lack of firm therapeutic ranges to the user. You should discuss both patient variability and test variability. For example:

> **No firm therapeutic range exists for cyclosporine [tacrolimus] in whole blood. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of cyclosporine, co-administration of other immunosuppressants, type of transplant, time post-transplant and a number of other factors contribute to different requirements for optimal blood levels of cyclosporine. Therefore, individual cyclosporine values cannot be, used as the sole indicator for making changes in treatment regimen and each patient should be thoroughly evaluated clinically before changes in treatment regimens are made. Each user must establish his or her own ranges based on clinical experience.**
>
> **Therapeutic ranges vary according to the commercial test used, and therefore should be established for each commercial test. Values obtained with different assay methods cannot be used interchangeably due to differences in assay methods and cross-reactivity witb metabolites, nor should correction factors be applied. Therefore, consistent use of one assay for individual patients is recommended.**

Performance Characteristics

You should describe the protocol and results for each performance characteristic discussed in Section 6. Protocol descriptions and results in the package insert should include all of the information cited in Section 6, including scatterplots of the new assay versus the reference (e.g., HPLC) method and, in some cases, graphs of inter-individual variation or equivalent information, in order to best represent results of the method comparison for the user. See also applicable sections in the NCCLS guidelines cited in Section 6 concerning statements of claims.

8. New Instrument Applications

For information concerning application of cleared or approved test systems to additional analyzers, see the guidance entitled "Data for Commercialization of Original Equipment Manufacturer, Secondary and Generic Reagents for Automated Analyzers," http://www.fda.gov/cdrh/ode/odecl950.html. The approach described in that guidance is appropriate in cases when performance characteristics on the new analyzer meet pre-determined acceptance criteria specified in a protocol submitted by the manufacturer and reviewed by the FDA. If performance characteristics do not meet pre-determined acceptance criteria, a new 5 1 O(k) (which may be an Abbreviated 5 1 O(k) is appropriate).

When the new analyzer is within the same family and does not involve any changes in reagents, sample treatment, or assay procedure that could potentially affect cross-reactivity or

partitioning of metabolites, it is sufficient for the method comparison studies in the protocol to include comparison of samples on the new instrument to the previously cleared instrument. In this case, results of the method comparison study of the original test system versus the HPLC reference procedure should still be available to the user in the package insert. In contrast, when application to a new analyzer does include changes in reagents, sample treatment or procedure, a method comparison study including HPLC should be included in the protocol for the add-to and results should be included in the labeling.

9. References

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